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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/462,993 | 04/17/2000 | MARIE-PAULE KIENY | 017753-122 | 5746 |

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| EXAMINER |
|---|
| LI, QIAN J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 19 |

DATE MAILED: 09/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/462,993 | KIENY ET AL. | |
| | Examiner | Art Unit | |
| | Janice Li | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *44-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

## DETAILED ACTION

The amendment filed on June 25, 2002 has been entered as Paper #18. Claims 21-43 have been canceled. Claims 44, 48, 51, 56, and 62 have been amended, claims 65-72 are newly added. Claims 44-72 are pending in the application, and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

### *Priority*

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Any nonprovisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications.

Receipt is acknowledged of papers concerning FR 97 09152, filed in France on July 18, 1997, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRIITEN DESCRIPTION REQUIREMENT

Claims 44-72 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66.

No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 47 recites an immunogenic polypeptide derived from *non-oncogenic variants* of E6 or E7 polypeptide of a papillomavirus. The specification fails to define the term or teach how to make and test for the variants so that the resulting polypeptide will not be oncogenic, and thus, fails to provide sufficient written description for the claimed invention.

An adequate written description for an active molecule requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structure and physical properties of the molecule itself. It is not sufficient to define the agents solely by its principal biological property, i.e. "non-oncogenic variants", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any variant with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all agents that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties of a chemical, or the sequences of a protein and nucleic acids, which provide the means for practicing the invention. The

court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Claims 44-72 are drawn to a composition comprising sequences derived from E6 and E7 of HPV, and homologous to SEQ ID No: 1 or 2, and method of using such composition. The specification defines homologous as "a degree of identity with said sequence greater than 70%..." (page 12, lines 5-9). Given the broadest reasonable interpretation, the claims embrace a genus of polypeptides that are identified with E6 or E7 with no limitation of sequence homology, or are identified with SEQ ID Nos: 1 and 2 by their sequence similarity of greater than 70%. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of their function, i.e. whether the genus of the polypeptides would function as SEQ ID Nos: 1 and 2, capable of enhancing a HPV16 specific antitumor response.

In view of the state of the art in protein biology, it is one of the most complex area of biochemistry. Considering the possible numbers of polypeptide variants, the art known knowledge is "EACH POSITION IN A PEPTIDE IS UNIQUELY DEFINED, THE NUMBER OF POSSIBLE PEPTIDES IS VERY LARGE, EVEN IN A RELATIVELY SHORT PEPTIDE. WHEN THE NUMBER OF AMINO ACID UNITS IN THE PEPTIDE CHAIN EQUALS *N*, THE NUMBER OF POSSIBLE PEPTIDES IS $20^N$. THE PREPARATION OF A SPECIFIC PEPTIDE SEQUENCE AND THE DETERMINATION OF THE SEQUENCE OF AMINO ACIDS IN A PEPTIDE OR PROTEIN CHAIN REQUIRES SPECIFICALLY ADAPTED CHEMICAL METHODS." (*Encyclopedia Britannica online*). It is highly unpredictable, based on

sequence homology alone, that sequence homologues will have the same activity as that protein to which they are being compared. This is because one cannot accurately predict the effects of the dissimilarities in the sequences identified by SEQ ID Nos: 1 and 2, and of putatively related family members upon protein structure and function. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein; and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. They also teach that the prediction of protein structure from sequence data, and in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1); that while it is known that many amino acid substitutions are possible in any given position, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). *Everett et al* (Nat Genetics 1997;17:411-22) use sophisticated computational modeling based on sequence homology to determine that the gene product causing Pendred syndrome was a sulphate transporter. However, subsequent research and investigation into the actual functional properties of the protein revealed that the protein was actually a chloride-iodide transporter and not a sulphate transporter as was originally predicted based on sequence homology (*Scott et al,* Nat Genetics 1999 Apr;21:440-443). *Bork*

(Genome Res 2000:10;398-400) teaches the power and pitfalls associated with comparative sequence analysis for predicting protein function, and points out that most prediction schemes extrapolate from current knowledge, and many bioinformatics methods have difficulty exceeding a 70% prediction accuracy, and in the example of *Marcotte et al*, the prediction error rate is 82% (see left column in page 400). *Rudinger* (Peptide Hormones 1976; June; pages 1-7) teaches the relationship of sequence components and the peptide hormone function "THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6).

Therefore, according to the current levels of the skill, determination of the effects of particular sequence changes is not predictable until they are actually made and used, hence resulting in a trial and error situation. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed. Since the specification fails to teach any one of polypeptide comprising 70% sequence homology with SEQ ID Nos: 1 and 2 would have an immune enhancing effect for tumors expressing HPV16 antigens, it fails to provide a sufficient written description for the genus of homologues of SEQ ID Nos: 1 and 2.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS",

"IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of homologues of SEQ ID Nos: 1 and 2 that are "antitumoral compositions". Therefore, only the described SEQ ID Nos: 1 and 2 meet the written description provision of 35 U.S.C. §112, first paragraph.

ENABLEMENT REQUIREMENT

The prior rejection of claims 44-64 has been modified which appears below.

The response and arguments (Paper #18) to the previous rejection (Paper #16) have been carefully considered but found not persuasive in the aspects related to following issues.

Claims 44-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing tumor cell-load in a subject comprising administering to the subject a composition comprising a non-integrative vector encoding

an immunogenic polypeptide fused with a cellular membrane-anchoring sequence, wherein said polypeptide is SEQ ID Nos: 1 and 2 derived from E6 or E7 early region of a papillomavirus genome, and wherein the *tumor cells express HPV16 antigen*, does not reasonably provide enablement for treatment of *any* type of cancer in a subject by administering to the subject the claimed composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

These claims are drawn to using the non-oncogenic derivatives and variants of E6 and E7 polypeptide, and homologues of SEQ ID Nos: 1 and 2, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the broad class of variants encompassed by the claims. Since the disclosure fails to describe the common attributes or characteristics that identify

members of the claimed genus, SEQ ID Nos: 1 and 2 alone is insufficient to describe the genus. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of the variants encompassed by these claims, thus except SEQ ID Nos: 1 and 2, one would not know how to use the invention without first carrying out undue experimentation to determine which of the variants would have antitumor function. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The method claims are drawn to treatment of cancer or tumor in a subject comprising administering a composition comprising a non-integrative vector encoding an immunogenic polypeptide derived from E6 or E7 early region of a papillomavirus genome fused with a cellular membrane sequence, wherein said polypeptide is derived from E6 or E7 region of a papillomavirus genome. Given the broadest reasonable interpretation, the claims embrace a method for treating any type of cancer using said composition.

In view of the guidance provided in the specification, it teaches inoculating BMK-16 myc tumor cells to C57BL mice and administering said composition three days later or immunizing mice three times before challenging the mice with E7W1 tumor cells, a protective effect was observed in both cases. The specification teaches that this effect is not observed in non-recombinant virus which expressing E6 or E7 mutants having a native nuclear location. The specification teaches that the modified immunogenic

proteins having a cell membrane location would enhance their accessibility to the host's immune system, whether it is specific or non-specific (page 3, lines 27-34). The specification teaches that both BMK-16 and E7W1 cells are transfected with either HPV16 genome or E7 region, therefore, the disclosed enhanced antit-umor response illustrates an antigen-specific host response. However, the specification fails to teach that the claimed composition could also enhance immune response to tumors expressing antigens other than HPV16, thus, fails to show a non-specific antitumor effects of claimed composition.

As cited in Office action Papers #13 and #16, the teachings of the skilled artisan *McCluskie et al*, *Bodey et al,* and *Radoja et al*, illustrated the under-developed and unpredictable state of the art pertinent to cancer therapy, and the state of the art is silent about the non-specific immune enhancing effect of E6 or E7 polypeptide of HPV16. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such non-specific immune enhancing effect of claimed composition. The disclosed specific immune enhancing effect of claimed composition is insufficient to support the broad claims of treatment for any type of tumor or cancer, thus, it is not enabled for its full scope because the art-recognized barriers in achieving successful cancer immunotherapy, and common knowledge in specific and non-specific immune response.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* antitumor effect for any type of cancer, in particular for the treatment of any and all cancers, the lack of direction or guidance provided by

the specification as well as the absence of working examples with regard to inducing a *non-specific* antitumor immune response, and the breadth of claims directed to the use of any non-oncogenic derivatives and variants of E6 or E7 of a papilomavirus, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44, 47, 50-52, 58, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 recites the limitation "said E6 or E7 polypeptide". There is insufficient antecedent basis for this limitation in the claim.

Claim 50 recites, "wherein said recombinant vector comprises, in addition, the sequences encoding at least one compound". The claim is vague and indefinite because a nucleic acid sequence could encode for a protein or a peptide, but not any compound.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 9, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER